REMARKS

Claims 16, 20-22, 24-31, 33-35, and 37-40 are currently pending. Claim 18 has been withdrawn from consideration. Claims 17, 19 and 32 have been cancelled. Claims 16, 20, and 37 have been amended. Claims 38-40 are new, and are supported by original claims 16, 34 and 37. Claims 16 and 37 have been amended to incorporate the elements of cancelled claim 19. Claim 20 has been amended so as not to depend from a cancelled claim. No new subject matter has been added. In addition to the remarks submitted in Amendment A, dated August 1, 2005, please consider the following remarks.

1. Rejection of the Claims under 35 U.S.C. §103(a) (¶3)

Reconsideration is respectfully requested of the rejection of claims 16-17, 19, 21, 22, 24-26, 30-34, and 37 under 35 U.S.C. § 103(a) as being obvious over Sato, et al. (U.S. Patent Application Publication No. 2003/0092622).

Amended claim 16 is directed to a stable pharmaceutical composition comprising erythropoietin and a peptide stabilizer. The peptide stabilizer is selected from the group consisting of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-His, Gly-Asp, Gly-Ala, Ala-Gly, Ala-Ala, derivatives thereof and mixtures thereof. The composition is free of serum albumin.

Sato, et al. describe a protein formulation containing a stabilizer selected from tryptophan, a tryptophan derivative or a salt thereof. The addition of the stabilizer is said to promote long-term storage stability of the protein formulation. One of the proteins that may be stabilized using the method described by Sato et al. is erythropoietin.

As stated in MPEP §2143, in order for the Office to show a prima facie case of obviousness, the Office must meet three criteria: (1) the prior art reference(s) must teach or suggest all of the claim limitations; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings; and (3) there must be some reasonable expectation of success.

As discussed above, the only stabilizers that Sato et al. describe are tryptophan, tryptophan derivatives, and salts thereof. Paragraph [0047] of Sato, et al. lists a large number of salts and derivatives that can be used, but, as can be seen from that list, the stabilizer described by Sato et al. always comprises the amino acid tryptophan or a derivative or salt thereof. Sato et al. do not suggest the use of any of the peptides listed in claim 16. In addition, there is no suggestion or motivation in Sato, et al. to use any of the peptides listed in claim 16 as stabilizers. Sato, et al. do not suggest that dipeptides or tripeptides generally would be effective stabilizers. Consequently, Sato, et al. would not have motivated one skilled in the art to use anything other than a tryptophan containing compound as a stabilizer. Sato, et al. thus do not teach or suggest all the limitations of claim 16.[1]

Claims 20-22, 24-26, 30, 31 and 33 depend either directly or indirectly from claim 16 and are thus patentable for the same reasons as claim 16, as well as for the additional elements they require.

Claim 34 is similar to amended claim 16, and further comprises a polyoxyalkylene sorbitan fatty acid ester. Claim 34 is patentable for the same reasons as set forth above for claim 16, as well as for the additional elements it requires.

As amended, claim 37 is similar to claim 16, and further requires that the composition be for administration by parenteral injection. Claim 37 is thus patentable for the same reasons as set forth above for claim 16, as well as for the additional elements it requires.

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[1]The Office has stated that the tryptophan derivatives of Sato, et al. constitute "derivatives" of the peptide stabilizers claimed in the present application because of similarity in structure (i.e., dipeptides or tripeptides having at least one amino acid in common) and ability to stabilize protein compositions. Applicants respectfully disagree, and submit that the stabilizers listed in amended claim 16 are entirely different peptides than the peptides disclosed in Sato, et al., not derivatives. For example, the peptides Gly-Ala and Ala-Ala (listed in amended claim 16) are different peptides, not derivatives of each other, even though they have at least one amino acid in common (e.g, Ala) and may both act as protein stabilizers. The same may be said for the peptides listed in amended claim 16 and the stabilizers disclosed in Sato, et al.

New claims 38-40 are similar to claims 16, 34 and 37 except that the peptide stabilizer is selected from the group consisting of tetrapeptides, pentapeptides, derivatives thereof and mixtures thereof. Sato et al. do not suggest the use of any of the peptides listed in claim 38 as stabilizers. Sato, et al. do not suggest that tetrapeptides or pentapeptides generally would be effective stabilizers. Consequently, Sato, et al. would not have motivated one skilled in the art to use anything other than a tryptophan containing compound as a stabilizer. Sato, et al. thus do not teach or suggest all the limitations of claim 38 or its dependent claims 39 and 40.

2. **Rejection of the Claims Under 35 U.S.C. §103(a) (¶4)**

Reconsideration is respectfully requested of the rejection of claims 24-29 and 35 under 35 U.S.C. § 103(a) as being obvious over Sato, et al. (U.S. Patent Application Publication No. 2003/0092622) in view of WO 02/14356.

Claims 24-29 and 35 depend either directly or indirectly from claims 16 and 34, respectively, as discussed above.

Sato, et al. is discussed above. WO 02/14356 discloses the preparation of erythropoietin omega and methods of treatment using the same.

The Office alleged that it would have been obvious to stabilize the erythropoietin omega of WO 02/14356 with a peptide stabilizer described by Sato, et al. to preserve its therapeutic activities. With respect to Sato, et al., Applicants again note that Sato, et al. only teach stabilizers selected from tryptophan, tryptophan derivatives and salts, and do not disclose or suggest that of any of the peptides listed in claim 16 or 34 or new claims 38-40 may be used to stabilize a composition comprising erythropoietin. Furthermore, WO 02/14356 does not teach or even mention that erythropoietin omega can be formulated using peptide stabilizers. There is therefore no motivation in the cited references to combine the teachings of Sato, et al. and WO 02/14356, absent the hindsight analysis of the Applicants' disclosure. Furthermore, even if the teachings of Sato, et al. were combined with the teachings of WO 02/14356, one skilled in the art would still not have arrived at the present invention, i.e., a stable pharmaceutical composition of

erythropoietin comprising a peptide stabilizer selected from the group consisting of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-His, Gly-Asp, Gly-Ala, Ala-Gly, Ala-Ala, which is free of serum albumin. Sato, et al. and WO 02/14356 thus either alone or in combination fail to teach or suggest all the limitations of the claims. Claims 24-29, 35 and new claims 38-40 are thus patentable over the combination of Sato, et al. and WO 02/14356.

3. **Rejection of the Claims Under 35 U.S.C. §103(a) (¶5)**

Reconsideration is respectfully requested of the rejection of claims 16, 17, 19, 21, 22, 24-26, 30-34, and 37 under 35 U.S.C. §103(a) as being obvious over WO 01/64241. As stated in the Office action, WO 01/64241 is the equivalent to the Sato, et al. reference discussed above, only published in Japanese. Applicants therefore submit that claims 16, 21-22, 24-26, 30-34, and 37-40 are patentable over WO 01/64241, for the same reasons as set forth above in §1 of this response, with respect to Sato, et al.

4. **Rejection of the Claims Under 35 U.S.C. §103(a) (¶6)**

Reconsideration is respectfully requested of the rejection of claims 24-29 and 35 under 35 U.S.C. §103(a) as being obvious over WO 01/64241 in view of WO 02/14356. As stated in the Office action, WO 01/64241 is the equivalent to the Sato, et al. reference discussed above, only published in Japanese. Applicants therefore submit that claims 24-29, 35 and new claims 38-40 are patentable over WO 01/64241 in view of WO 02/14356, for the same reasons as set forth above in §2 of this response, with respect to Sato, et al. and WO 02/14356.

5. **Rejection of the Claims Under 35 U.S.C. §103(a) (¶7)**

Reconsideration is respectfully requested of the rejection of claims 16-17, 19-22, 24, and 37 under 35 U.S.C. § 103(a) as being obvious over Cormier, et al. (U.S. Patent Application Publication No. 2002/0058608).

Cormier et al. teach a buffered aqueous formulation for transdermal electrotransport delivery, which comprises a therapeutic agent buffered with a dipeptide buffer. According to Cormier et al., a therapeutic agent formulated in this manner can be selected from a vast number of different compounds, ranging from antibiotics, antiviral agents, anesthetics and antimigraine agents to proteins, peptides, hormones and muscle relaxants (see paragraph [0033]). The list of proteins and peptides that are said to be applicable embraces **over 90 agents**, including erythropoietin (see paragraph [0034]). However, Cormier, et al. only exemplified formulations of human growth hormone, synthetic radiolabeled decapeptide (DECAD), and small molecular weight drug-like compounds such as trimethylammonium bromide (TMAB) and sodium methanesulfate (SMS) in the working examples of the patent. Furthermore, according to Cormier, et al., the dipeptide buffer is preferably selected from a list of **over 55** dipeptides, including Gly-Asp and Gly-His (see paragraph [0014]). No tetrapeptides or pentapeptides are exemplified.

The Office has stated that it would have been obvious to administer EPO using the Gly-His buffer of Cormier et al. because the reference discloses that EPO is a protein which can be usefully administered in their formulations.

Initially, applicants note that in order to arrive at a composition comprising erythropoietin and Gly-His,[2] one skilled in the art must pick and choose from several options in Cormier, et al. Specifically, one skilled in the art would have to choose erythropoietin from a laundry list of **over 90** possible drugs listed by Cormier, et al. After deciding to include erythropoietin, one skilled in the art would then have to choose Gly-His from **over 55** possible dipeptides listed by Cormier, et al. Furthermore, these choices must be made absent any teaching or suggestion in Cormier, et al. as to the specific combination of erythropoietin and Gly-His (or Gly-Asp). As

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[2]Applicants note that the only dipeptides listed in claim 16 that are specifically disclosed by Cormier, et al. are Gly-His and Gly-Asp. Cormier, et al. fail to teach or suggest the use of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-Ala, Ala-Gly, or Ala-Ala as buffers. Furthermore, there would be no motivation to use any of these peptides in the compositions of Cormier, et al., since Cormier, et al. state that the preferred dipeptides are dipeptides that contain His.

such, applicants submit that there is no suggestion or motivation in Cormier, et al. to formulate a composition comprising the specific combination of erythropoietin and Gly-His (or Gly-Asp) from about 5,000 combinations that could have been made.

Furthermore, even if one skilled in the art attempted to formulate a composition comprising erythropoietin and Gly-His (or Gly-Asp), one may still not have arrived at a stable pharmaceutical composition as defined in claim 16. For example, claim 16 also requires the composition be free of serum albumin. There is no teaching or suggestion in Cormier, et al. that their compositions are formulated so as to be free of serum albumin. The Office has stated that the reason Cormier, et al. do not mention serum albumin is because their compositions do not comprise serum albumin. Applicants interpret this statement as an assertion that the compositions of Cormier, et al. are inherently free of serum albumin. Applicants respectfully disagree. A finding of inherency cannot be based on mere assumptions by the Office. Rather, to establish inherency, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art."[3] Furthermore, "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic."[4] Therefore, just because serum albumin is not mentioned by Cormier, et al. does not mean that the compositions of Cormier, et al. are necessarily free of serum albumin. As such, applicants submit that Cormier, et al. fail to teach or suggest all the limitations of claim 16.

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[3]MPEP §2112 (citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

[4]MPEP §2112 (citing *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993)). MPEP §2112 also states "[i]nherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." (quoting *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999).

Claims 20-22, and 24 depend either directly or indirectly from claim 16 and are therefore patentable over Cormier, et al. for the same reasons as set forth above for claim 16, as well as for the additional elements they require.

As discussed above, amended claim 37 is similar to claim 16, except further requires the composition be for administration by parenteral injection. Claim 37 is thus patentable for the same reasons as set forth above for claim 16. In addition, applicants note that the composition of amended claim 37 is for administration by parenteral injection. In contrast, the formulations of Cormier, et al. are for transdermal delivery. There is no teaching or suggestion in Cormier, et al. of using their formulations for administration by parenteral injection, nor is there any teaching or suggestion of how a formulation for parenteral injection would be prepared or stabilized. As such, the cited reference fails to teach or suggest all the limitations of claim 37.

Furthermore, there is no suggestion or motivation to modify Cormier, et al. to arrive at the invention of claim 37. As discussed above, there is no teaching or suggestion in Cormier, et al. of using their formulations for administration by parenteral injection. In fact, if anything, Cormier, et al. teach away from administration by parenteral injection. For example, Cormier, et al. specifically point out drawbacks of parenteral injection, stating:

> Polypeptide and protein molecules are highly susceptible to degradation by proteolytic enzymes in the gastrointestinal tract and are subjected to an extensive hepatic metabolism when taken orally. Thus, these substances usually require parenteral administration to achieve therapeutic levels in the patient's blood. The most conventional parenteral administration techniques are hypodermic injections and intravenous administration. Polypeptides and proteins are, however, inherently short acting in their biological activity, requiring **frequent injections**, often several times a day, to maintain the therapeutically effective levels needed. Patients frequently find this treatment regimen to be **inconvenient and painful**. Such therapy also includes **risk of, e.g., infection.**[5]

[5]Cormier, et al., p. 1, ¶0007.

One skilled in the art would not have been motivated by Cormier, et al. to modify the formulations of Cormier, et al. for administration by parenteral injection. Claim 37 is thus also patentable over the cited reference for this additional reason.

As for new independent claim 38, in order to arrive at a composition comprising erythropoietin and a tetrapeptide or pentapeptide, one skilled in the art would have to choose erythropoietin from a laundry list of over 90 possible drugs listed by Cormier, et al. After deciding to include erythropoietin, one skilled in the art would then have to choose a tetrapeptide or pentapeptide rather than the over 55 possible dipeptides listed by Cormier, et al. Furthermore, these choices must be made absent any teaching or suggestion in Cormier, et al. as to the specific combination of erythropoietin and a tetrapeptide or pentapeptide. As such, applicants submit that there is no suggestion or motivation in Cormier, et al. to formulate a composition comprising the specific combination of erythropoietin and a tetrapeptide or pentapeptide from the combinations that could have been made. As such, applicants submit that Cormier, et al. fail to teach or suggest all the limitations of claim 38. Claims 39 and 40, which depend from claim 38, are patentable for these reasons and those advanced above for claims 34 and 37, respectively.

6. **Rejection of the Claims Under 35 U.S.C. § 103(a) (¶8)**

Reconsideration is respectfully requested of the rejection of claims 24-29 under 35 U.S.C. § 103(a) as being obvious over Cormier, et al. (U.S. Patent Application Publication No. 2002/0058608) and further in view of WO 02/14356.

Claims 24-29 depend either directly or indirectly from claim 16, which is discussed above. Cormier, et al. and WO 02/14356 are discussed above.

The Office has alleged that it would have been obvious to formulate the erythropoietin omega of WO 02/14356 in the compositions of Cormier, et al. because it would be desirable to administer erythropoietin omega iontophoretically, and Cormier, et al. teach administration of a wide range of proteins. Claims 16 and 38 are patentable over Cormier, et al. for the reasons set forth above. Specifically, there is no suggestion or motivation in Cormier, et al. to formulate a

composition comprising the specific combination of erythropoietin and any of the peptides listed in claim 16 or 38. Furthermore, Cormier, et al. fail to teach or suggest all the limitations of claim 16 or 38. The deficiencies of Cormier, et al. are not overcome by WO 02/14356 since, as discussed above, WO 02/14356 does not even disclose or suggest that erythropoietin omega can be formulated using peptide stabilizers. Therefore, even if one were to combine Cormier, et al. and WO 02/14356, one still would not arrive at a composition as defined by claim 16 or 38. Applicants thus submit that claims 16 and 38 are patentable over of Cormier, et al. and WO 02/14356 either alone or in combination. Since claims 24-29 and 39-40 depend either directly or indirectly from claim 16 or 38, they are patentable for the same reasons as set forth above for claim 16 or 38.

7. **Rejection of the Claims Under 35 U.S.C. § 103(a) (¶9)**

Reconsideration is respectfully requested of the rejection of claims 30-31 and 33-34 under 35 U.S.C. §103(a) as being obvious over Cormier, et al. (U.S. Patent Application Publication No. 2002/0058608) and further in view of Holladay, et al. (U.S. Patent No. 6,328,728).

Claims 30-31 and 33 depend either directly or indirectly from claim 16, which is discussed above, and further call for the composition to comprise a surfactant.

Cormier, et al. is discussed above.

Holladay et al. teach a method of enhancing electrotransport delivery of an active agent, such as a protein in the presence of at least one electrotransport enhancer selected from nonionic surfactants, zwitterionic surfactants lacking a net charge, and mixtures thereof, such as polyoxyethylene (20) sorbitan monolaurate or polyoxyethylene (20) sorbitan monopalmitate.

The Office has stated that it would have been obvious to one of ordinary skill in the art to include a surfactant of Holladay, et al. in the compositions of Cormier, et al. to increase the flux or decrease biodegradation of proteins during electrotransport delivery.

Claim 16 is patentable over Cormier, et al. for the reasons set forth above. Specifically, there is no suggestion or motivation in Cormier, et al. to formulate a composition comprising the specific combination of erythropoietin and any of the peptides listed in claim 16. Furthermore, Cormier, et al. fail to teach or suggest all the limitations of claim 16. The deficiencies of Cormier, et al. are not cured by the teachings of Holladay, et al., since Holladay, et al. do not teach or suggest the use of peptides in their compositions. Rather, Holladay, et al. merely teach enhancing electrotransport delivery of an active agent, such as a protein, in the presence of at least one electrotransport enhancer, such as certain surfactants. Motivation for formulating a composition comprising the specific combination of erythropoietin and one of the peptides listed in claim 16 can thus not be found in Holladay, et al.

Claims 30-31 and 33 depend either directly or indirectly from claim 16 and are thus patentable for the same reasons as set forth above for claim 16, as well as for the additional elements they require.

As discussed above, claim 34 is directed to a stable pharmaceutical composition comprising erythropoietin, a polyoxyalkylene sorbitan fatty acid ester, and a peptide stabilizer. The peptide stabilizer is selected from the group consisting of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-His, Gly-Asp, Gly-Ala, Ala-Gly, Ala-Ala, derivatives thereof and mixtures thereof, and the composition is free of serum albumin.

For the reasons set forth in §5 above with respect to Cormier, et al., there is no suggestion or motivation in Cormier, et al. to formulate a composition comprising the specific combination of erythropoietin and Gly-His or Gly-Asp (or Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-Ala, Ala-Gly, or Ala-Ala, which are not even mentioned in Cormier, et al. as buffers). The deficiencies of Cormier, et al. are not cured by the teachings of Holladay, et al., since, as discussed above, Holladay, et al. do not teach or suggest the use of peptides in their compositions.

Furthermore, Cormier, et al. do not disclose that their composition may comprise a polyoxyalkylene sorbitan fatty acid ester, as required by claim 34. At most, Cormier, et al. state

that surfactants may be used as a penetration enhancer to facilitate absorption through the skin.[6] Holladay, et al. disclose a list of **over 35** non-ionic and zwitterionic surfactants that may be used as penetration enhancers, including polyoxyethylene (20) sorbitan monolaurate and polyoxyethylene (20) sorbitan monopalmitate. In order to formulate a composition comprising erythropoietin and Gly-His (or Gly-Asp) and a polyoxyalkylene sorbitan fatty acid ester, one skilled in the art would therefore have to choose erythropoietin from a laundry list of **over 90** possible drugs listed by Cormier, et al. and Holladay, et al., and, after deciding to include erythropoietin, one skilled in the art would then have to choose Gly-His or Gly-Asp from **over 55** possible dipeptides listed by Cormier, et al., and would then have to further choose a polyoxyalkylene sorbitan fatty acid ester from **over 35** possible surfactants listed by Holladay, et al. Furthermore, these choices must be made absent any teaching or suggestion in Cormier, et al. or Holladay, et al. as to the specific combination of erythropoietin, Gly-His or Gly-Asp, and a polyoxyalkylene sorbitan fatty acid ester. As such, applicants submit that there is no suggestion or motivation in Cormier, et al. or Holladay, et al. to formulate a composition comprising the specific combination of erythropoietin, Gly-His or Gly-Asp, and a polyoxyalkylene sorbitan fatty acid ester since these combinations are only two of over 100,000 combinations that could have been made.

Furthermore, even if one skilled in the art attempted to formulate a composition comprising erythropoietin and Gly-His or Gly-Asp and a polyoxyalkylene sorbitan fatty acid ester based on the teachings of Cormier, et al. and Holladay, et al., one may still not have arrived at a stable pharmaceutical composition as defined in claim 34, since there is no teaching or suggestion in Cormier, et al. or in Holladay, et al. that their compositions are formulated so as to be free of serum albumin, as required by claim 34. Neither Cormier, et al. nor Holladay, et al. mention serum albumin. As discussed above, just because serum albumin is not mentioned by Cormier, et al. or Holladay, et al. does not mean that the compositions of Cormier, et al. or

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[6]Cormier, et al. at p. 4, ¶0035.

Holladay, et al. are necessarily free of serum albumin. As such, applicants submit that Cormier, et al. and Holladay, et al., either alone or in combination, fail to teach or suggest all the limitations of claim 34.

New claims 38-40 are also patentable over this combination of references for the same reasons advanced above.

8. **Rejection of the Claims Under 35 U.S.C. § 103(a) (¶10)**

Reconsideration is respectfully requested of the rejection of claim 35 under 35 U.S.C. §103(a) as being obvious over Cormier, et al. (U.S. Patent Application Publication No. 2002/0058608) in view of WO 02/14356 and further in view of Holladay, et al. (U.S. Patent No. 6,328,728).

Claim 35 depends from claim 34, discussed above, and further states that the erythropoietin is erythropoietin omega. For the reasons previously noted, claim 34 is patentable over Cormier, et al. and Holladay, et al. either alone or in combination.

The Office has stated that it would have been obvious to one of ordinary skill to include the surfactant of Holladay, et al. in the composition of Cormier, et al. as modified to include the EPO omega of WO 02/14356 to increase the flux or decrease biodegradation of proteins during electrotransport delivery. With respect to Cormier, et al. and Holladay, et al. applicants again note that there is no suggestion or motivation in Cormier, et al. or Holladay, et al. to formulate a composition comprising the specific combination of erythropoietin, Gly-His or Gly-Asp (or Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-Ala, Ala-Gly, or Ala-Ala), and a polyoxyalkylene sorbitan fatty acid ester. Nor do Cormier, et al. and Holladay, et al., either alone or in combination, teach or suggest all the limitations of claim 34. The deficiencies of Cormier, et al. and Holladay, et al. are not overcome by WO 02/14356 since, as discussed above, WO 02/14356 does not even disclose or suggest that erythropoietin omega can be formulated using peptide

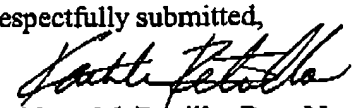
stabilizers. Furthermore, even if one were to combine Cormier, et al., Holladay, et al., and WO 02/14356, one still would not arrive at a composition as defined by claim 35. Applicants thus submit that claim 35 is patentable over Cormier, et al., Holladay, et al., and WO 02/14356 either alone or in combination.

CONCLUSION

In view of the foregoing comments, Applicants respectfully request entry of the amendments and solicit allowance of the claims.

The Commissioner is hereby authorized to charge the amount of $200.00 for one additional independent claim to Deposit Account No. 19-1345. Please charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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